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Aldosteronism

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Abstract—We performed a prospective head-to-head comparison of the accuracy of the captopril test (CAPT) and the saline infusion test (SAL) for confirming primary aldosteronism due to an aldosterone-producing adenoma (APA) in patients with different sodium intake. A total of 317 (26.9%) of the 1125 patients screened in the Primary Aldosteronism Prevalence in Italy Study underwent both CAPT and SAL. They were composed of the patients with a high aldosterone/renin ratio baseline and 1 every 4 patients without such criterion. The accuracy of post-CAPT or post-SAL plasma aldosterone values for diagnosing APA was estimated with the area under the receiver operator characteristics curves. Primary aldosteronism was found in 120 patients, of which 46 had an APA. No untoward effect occurred with either test. The area under the receiver operator characteristics curve of plasma aldosterone for both tests was higher ($P<0.0001$) than that under the diagonal, but the between-test difference was borderline significant ($P=0.054$). The optimal aldosterone cutoff value for identifying APA was 13.9 and 6.75 ng/dL for the CAPT and SAL, respectively. Even at these cutoffs, sensitivity and specificity were moderate because of overlap of values between patients with and without APA. When examined in relation to sodium intake, the accuracy of the SAL surpassed that of the CAPT in the patients with a sodium intake ≤130 mEq per day; this difference waned at a higher Na^+ intake. Thus, both the CAPT and the SAL are safe and moderately accurate for excluding APA; at a sodium intake >7.6 g per day, the SAL offers no advantage over the easier-to-perform CAPT. (*Hypertension*. 2007;50:424-431.)

Key Words: secondary hypertension ■ aldosterone ■ aldosteronism ■ clinical science ■ secondary

The Primary Aldosteronism Prevalence in Italy (PAPY) Study showed that primary aldosteronism (PA) is far more common than usually perceived: 11.2% of 1125 newly diagnosed hypertensive patients referred to hypertension (HT) centers had PA, which was because of an aldosterone-producing adenoma (APA) in 4.8% of the subjects.[1] The potential curability and prevention of excess cardiovascular damage (reviewed in Reference 2) and events[3] also underscores the importance of developing accurate strategies for timely diagnosing of APA.

The aldosterone/renin ratio (ARR) and the multivariable approaches proposed to this end are sensitive but moderately accurate,[4–6] because they do not completely differentiate patients with PA and those with primary (essential) HT (PH), as initially believed.[7] The ARR allows discrimination of patients with PA from those with low-renin PH only if aldosterone is overtly increased despite a high sodium (Na^+)

intake, provided that low or very low plasma renin activity can be accurately measured, which is rarely feasible in current laboratory practice.[8–12] Moreover, calculation of the ARR under some antihypertensive medications,[13] like β-adrenergic blockers,[14,15] which blunt renin but have little effect on aldosterone secretion, can generate false-positive ARR, thus further lowering its specificity.[9,16]

Identification of APA and unilateral hyperplasia, the surgically curable forms of PA, requires adrenal vein sampling (AVS), which is invasive and minimally risky.[17,18] Hence, a confirmatory test is necessary in the patients with a positive screening test to select candidates for AVS.[19] Available confirmatory tests are composed of the oral sodium loading test,[20] the saline infusion test (SAL),[21,22] the captopril test (CAPT),[4,23,24] or the fludrocortisone suppression test.[21,25–28] Their validation stands on studies on few patients with APA, mostly performed retrospectively, and with another test as

referent.[10,13,22,26] To date, only one study has compared the performance of the CAPT test with the oral Na^+ loading,[20] and although in one of the studies that introduced the CAPT the SAL was used as referent,[24] there was no head-to-head comparison of the CAPT and the SAL. Moreover, notwithstanding the well-known inverse relationship between renin and aldosterone secretion on one hand and Na^+ intake on the other, there is no information on the impact of Na^+ balance on either test performance.

The diagnostic performance of a test can be evaluated with a conclusive diagnosis as referent, which is feasible only in APA, because there are no criteria for reliably diagnosing idiopathic hyperaldosteronism (IHA). Therefore, the PAPY Study Steering Committee planned to prospectively compare the performance of the CAPT and SAL for excluding APA and to evaluate the effect of Na^+ intake on this performance.

Subjects and Methods

The PAPY Study protocol followed the Statement for Reporting Studies of Diagnostic Accuracy recommendations,[29] as detailed.[1] The procedures followed were in accordance with institutional guidelines; the protocol was approved by the institutional review committee of the University of Padua and adhered to the principles of the Declaration of Helsinki. An informed written consent was obtained from each participant.

Briefly, consecutive, newly diagnosed hypertensive patients, referred to specialized HT centers nationwide in Italy, were enrolled after an informed consent was obtained.[1] A previous diagnosis of a secondary form of HT and the patient's refusal to participate in the study were the exclusion criteria.

The CAPT and the SAL

The flow chart shown in Figure 1 summarizes the study protocol. All of the patients underwent measurement of the 24-hour Na^+ urine excretion. The CAPT was performed in the sitting position with 50 mg of PO captopril.[1] For the head-to-head comparison of the 2 tests, those who had an ARR ≥40 baseline, and/or ≥30 after captopril, and/or a logistic discriminant function score ≥0.50 (please see supplemental data available at http://hyper.ahajournals.org) and 1 of every 4 consecutive patients not fulfilling such criteria underwent the SAL.

For calculation of the ARR, the lowest value of the denominator, eg, plasma renin activity (PRA), was set to 0.2 ng/mL per hour to avoid overinflating the ARR. For both tests, patients were prepared from the pharmacological standpoint as described (data supplement).[1] Treatment with a long-acting calcium channel blocker and/or doxazosin was allowed if necessary for minimizing the risks of uncontrolled HT. The SAL was performed only when serum K^+ levels were ≥3.0 mEq/L, because hypokalemia blunts aldosterone secretion and, therefore, might preclude the detection of suppressibility of aldosterone with volume expansion. Thus, oral potassium supplementation was allowed during the days before the SAL.

The SAL involved infusion of 2 L of 0.9% saline IV over 4 hours.[21] Before and 4 hours after the infusion, PRA, plasma aldosterone, cortisol, and serum K^+ were measured (see the data supplement).

Further Tests

To avoid biasing the test performance evaluation, the further diagnostic workup (Figure 1) was based only on the results of ARR baseline, and/or after the CAPT, and/or the logistic discriminant function test[4] (see the data supplement).[1] The patients positive at such tests were submitted to an imaging test for identification of adrenocortical nodules,[1] but they were also submitted to AVS[17] or to dexamethasone-suppressed adrenocortical scintigraphy to identify a lateralized aldosterone excess production, regardless of the imaging test results.[1] AVS was deemed to provide a lateralization diagnosis only if bilaterally selective[17]; corticotropin stimulation was not systematically used during AVS, because although it improves assessment of selectivity of catheterization, it does not improve the diagnostic accuracy.[30,31]

Biochemical Measurements

Serum creatinine, serum and urine Na^+ and K^+ levels, PRA, aldosterone, cortisol, and glomerular filtration rate were measured as described[1]; hypokalemia was defined as serum K^+ ≤3.5 mEq/L. Normal ranges, intra-assay and interassay coefficients of variation, and antibody cross-reactivity for the hormonal measurements have already been reported.[1]

Diagnostic Criteria

Identification of APA required all of the following criteria: (1) evidence of PA at the screening test as defined above; (2) lateralization of aldosterone secretion at AVS or at ^{131}I-norcholesterol dexamethasone–suppressed adrenocortical scintigraphy; (3) evidence of adenoma at computed tomography, and/or magnetic resonance, and/or surgery, and/or pathology; and (4) demonstration of normokalemia and HT cure, or improvement, at follow-up after adrenalectomy by the criteria (see the data supplement) already
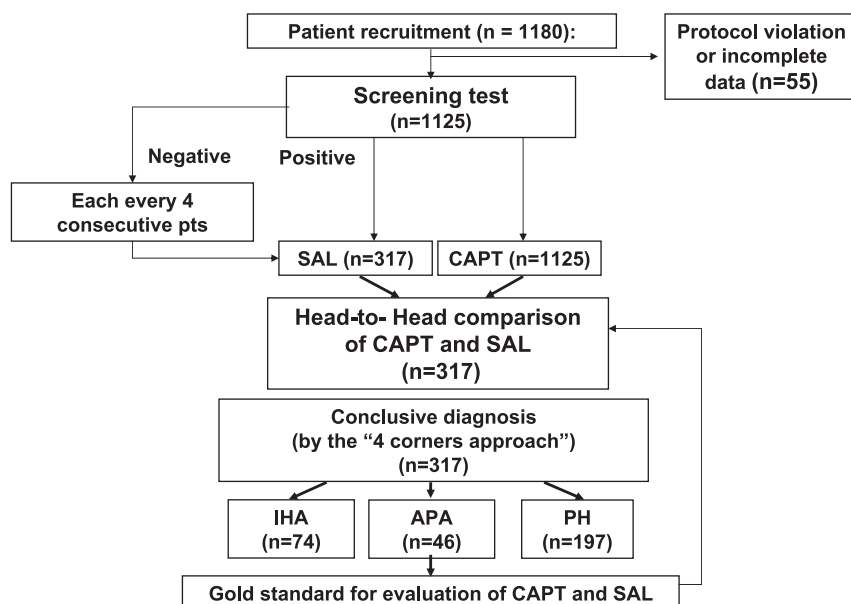
Figure 1. The flow chart shows the study design. After enrollment, 55 patients were discarded from further analysis because of incomplete data, protocol violations, or unwillingness to undergo further testing. The remaining 1125 patients undergoing measurement of the ARR baseline also had the CAPT. Those with an ARR ≥40 baseline, and/or ≥30 after captopril, and/or a logistic discriminant function score ≥0.50 (see the data supplement) and 1 every 4 consecutive patients not fulfilling this criterion were submitted to the SAL. The conclusive diagnosis of APA, as defined in Diagnostic Criteria, (and the presumed diagnosis of IHA) was then used for the purpose of assessing the diagnostic performance of the CAPT and SAL in the 317 patients who underwent both tests.

TABLE 1. Anthropometric and Biochemical Characteristics of the Patients With PH and With PA Caused by an APA and an IHA

Variable	PH	P	APA	P	IHA	P (IHA vs PH)
Age, y	46±11	0.031	51±13	NS	48±11	NS
BMI, kg m^{-2}	27.4±4.7	NS	27.4±4.1	NS	26.9±4.1	NS
Systolic BP, mm Hg	147±18	0.002	158±23	NS	153±16	0.066
Diastolic BP, mm Hg	97±11	NS	97±10	NS	100±10	0.035
Serum K$^+$, mEq L^{-1}	4.1±0.4	<0.0001	3.4±0.5	<0.0001	3.9±0.4	0.028
Na^+_uV, mEq day^{-1}	145 (135 to 155)	NS	131 (110 to 153)	NS	136 (122 to 151)	NS
GFR, mL min^{-1}	90±20	NS	84±16	NS	90±20	NS
PRA, ng mL^{-1} h^{-1}	1.31 (1.00 to 1.63)	0.002	0.64 (0.31 to 0.98)	NS	0.52 (0.37 to 0.68)	<0.001
Plasma aldosterone, ng dL^{-1}	17.9 (16.3 to 19.6)	<0.0001	32.1 (26.0 to 38.2)	NS	25.6 (22.4 to 28.8)	<0.0001
ARR, (ng dL^{-1})/(ng mL^{-1} h^{-1})$^{-1}$	13.7 (12.2 to 16.3)	<0.0001	50.2 (26.5 to 123.2)	NS	49.2 (32.9 to 77.8)	<0.0001
Plasma cortisol, nmolL^{-1}	146 (137 to 154)	NS	131 (120 to 143)	NS	143 (130 to 156)	NS

Data are mean±SD or 95% CI, in parentheses, for variables not normally distributed. BMI indicates body mass index; Na^+_uV, sodium urinary excretion; ARR, aldosterone (ng dL^{-1})/PRA (ng mL^{-1} h^{-1}) ratio; NS, not significant.

described.[1] Patients with PA but without conclusive evidence for a lateralized aldosterone excess were presumed to have IHA.

Statistical Analysis

A normal distribution was attained by appropriate transformations of skewed variables as PRA, aldosterone, and cortisol. One-way ANOVA followed by Bonferroni's test posthoc was used to compare quantitative variables between groups. Categorical variables distribution was investigated by χ^2 analysis; correlation was assessed by nonparametric Spearman test. Significance was set at $P<0.05$.

The cutoff values that gave the highest accuracy, eg, the best combination of sensitivity and false-positive rate, were determined by the plot of sensitivity/specificity versus criterion value. We assessed the accuracy of the CAPT and SAL for identifying APA, IHA, and PA at large by the area under the receiver operator characteristics (ROC) curve (AUC). The AUC can be interpreted as the average value of sensitivity for all of the possible values of specificity or the average value of specificity for all of the possible values of sensitivity. When the ROC curve coincides with the diagonal line, the AUC is equal to 0.50, and, therefore, the test cannot discriminate between groups; when there is no value overlapping between the groups, the AUC equals 1, and the ROC curve reaches the upper left corner of the plot. The ROC curves comparison was performed with the MedCalc software 8.1.1.0 (MedCalc Software).

Power of the Study

With 197 patients with PH and 46 with APA, and with this pairwise within-patient design, the study had a power >95% to investigate the accuracy of the CAPT and the SAL for diagnosing APA. For details on power calculation, please see the data supplement.

Results

Baseline Characteristics

The baseline features of the patients, divided by diagnosis, are shown in Table 1. The APA patients were older, had higher systolic blood pressure (BP), and also had baseline plasma aldosterone and ARR, whereas renin and K$^+$ levels were lower than in the PH patients. The 74 patients presumed to have IHA did not differ from the APA patients for baseline plasma aldosterone, PRA, and cortisol levels, although serum K$^+$ was higher and ARR lower than in the APA patients. The SAL was performed, on average, 4 weeks after the screening; however, there were no significant differences among the

PRA, aldosterone, cortisol, and ARR baseline values measured at the screening test and at the SAL.

At the time of the CAPT and SAL, 41% of the patients were untreated, 35% were on a calcium channel blocker or doxazosin, and 24% were on both agents. The APA patients required more often than the other groups (42%) a combination of calcium channel blocker or doxazosin to achieve BP control. Baseline PRA, aldosterone, and cortisol, either within the entire cohort or in each diagnosis group, did not differ across treatment groups.

CAPT

Captopril lowered BP but caused no symptomatic hypotension and adverse effects. It increased PRA in all of the groups (Table 2); post-CAPT PRA was higher in the PH than in the APA and IHA groups ($P<0.05$) but did not differ between APA and IHA. Aldosterone and cortisol concentrations fell in all of the groups. Aldosterone was higher in APA and IHA than in the PH group (both $P<0.0001$), albeit with a values overlap.

The fall of aldosterone after CAPT showed no correlation with the increase of PRA in any diagnosis group. It correlated with the fall of cortisol in the all cohort ($\rho=0.240$; $P<0.001$) and in the PH group ($\rho=0.181$; $P=0.05$) but not in the APA and IHA groups.

SAL

A raise of BP was occasionally seen with SAL, but no adverse effects and no change of serum K$^+$ occurred (Table 2). The SAL lowered PRA, aldosterone, and cortisol concentrations significantly without differences across diagnosis and treatment groups. The post-SAL aldosterone was higher in the APA and the IHA than in the PH group (both $P<0.0001$), albeit with a values overlap. By contrast, there were no significant differences of PRA and cortisol. The fall of aldosterone post-SAL correlated with that of PRA in the all cohort ($\rho=0.177$; $P<0.001$), the PH ($\rho=0.304$; $P=0.001$), and APA ($\rho=0.396$; $P=0.030$) groups but not in the IHA group ($\rho=0.253$; P not significant). The fall of aldosterone correlated with that of cortisol in the all cohort ($\rho=0.450$; $P<0.001$), the PH

TABLE 2.   Changes of PRA, Aldosterone, and Cortisol Observed After the Saline Infusion in Patients With PH and PA Caused by an APA and an IHA

Variable	APA		IHA		PH	
	Before	After	Before	After	Before	After
Captopril						
PRA, ng mL^{-1} h^{-1}	0.64 (0.31 to 0.98)	1.15 (0.54 to 1.76)†	0.52 (0.36 to 0.68)	0.82 (0.55 to 1.09)‡	1.31 (0.99 to 1.63)	3.32 (2.39 to 4.26)§
Plasma aldosterone, ng dL^{-1}	32.4 (26.7 to 39.1)	22.7 (18.4 to 27.0)§	24.2 (20.7 to 27.6)	20.9 (18.4 to 23.4)§	15.2 (13.5 to 16.9)	11.4 (10.4 to 12.4)§
Plasma cortisol, nmol L^{-1}	131 (120 to 143)	97 (87 to 106)§	143 (130 to 156)	120 (107 to 133)§	146 (137 to 154)	125 (116 to 133)§
Saline						
PRA, ng mL^{-1} h^{-1}	0.76 (0.42 to 1.09)	0.39 (0.21 to 0.56)*	0.65 (0.44 to 0.87)	0.34 (0.22 to 0.46)§	1.39 (1.03 to 1.76)	0.81 (0.55 to 1.07)§
Plasma aldosterone, ng dL^{-1}	32.4 (25.6 to 39.1)	17.6 (13.4 to 21.9)§	24.1 (20.7 to 27.6)	11.1 (8.6 to 13.6)§	15.2 (13.5 to 16.9)	5.5 (4.9 to 6.1)§
Plasma cortisol, nmol L^{-1}	93 (68 to 117)	52 (35 to 70)§	88 (63 to 112)	51 (36 to 67)§	101 (91 to 111)	63 (56 to 70)§

*$P<0.05$; †$P<0.01$; ‡$P=0.003$; §$P<0.001$ vs before each test.

($\rho=0.522$; $P<0.001$), the APA ($\rho=0.485$; $P=0.003$), and the IHA ($\rho=0.372$; $P=0.005$) groups.

Diagnostic Accuracy of the CAPT and SAL

Table 3 shows the AUC of plasma aldosterone after the CAPT and SAL and the optimal cutoff values for diagnosing APA, IHA, and PA in the all cohort. Because the AUC under the ROC curve was higher ($P<0.0001$) than that under the diagonal, both tests were useful to make all 3 of the diagnoses. For both the CAPT (0.769 ± 0.042) and the SAL (0.854 ± 0.030), the accuracy was highest for identification of APA and lowest for identification of IHA in the all cohort.

The optimal cutoff values of aldosterone were higher for post-CAPT than for post-SAL, suggesting that within the (different) time courses of these tests, the latter provides a more potent suppression of aldosterone secretion. However, for both tests, they generally fell in a narrow range. Post-CAPT plasma aldosterone value of 13.9 ng/dL, which corre-

sponded with the highest accuracy for identification of APA, furnished only moderate sensitivity (69.6; 95% CI: 54.2 to 82.2) and specificity (74.0; 95% CI: 67.2 to 80.0). The sensitivity (82.6; 95% CI: 68.6 to 92.2) and the specificity (75.1; 95% CI: 68.5 to 81.0) were slightly higher for the post-SAL at the plasma aldosterone value of 6.75 ng/dL that represents the highest point estimate of accuracy for identification of APA. The between-tests difference of accuracy was only borderline significant ($P=0.054$; Figure 2). Practically identical conclusions were reached when the analysis was confined to the centers that could perform AVS.[1]

The CAPT and SAL End Points

To investigate whether the PRA- or cortisol-corrected aldosterone values could improve the diagnostic accuracy over the raw plasma aldosterone values, we measured the AUC under the ROC curve for identification of APA of the PRA- and cortisol-corrected aldosterone values after CAPT and SAL. We found no significant increase of the AUC between the raw and the PRA- or cortisol-adjusted aldosterone values (data not shown) for either test.

TABLE 3.   Results of the ROC Curve Analysis for Post-CAPT and Post-SAL PA Concentration

Diagnosis	Patients	AUC (95% CI)	P	Optimal Cutoff, ng/dL
PA				
Saline	n=317	0.811 (0.764 to 0.859)	NS	6.80
Captopril		0.785 (0.734 to 0.836)		13.40
APA				
Saline	n=243	0.853 (0.794 to 0.912)	0.054	6.75
Captopril		0.765 (0.680 to 0.849)		13.90
IHA				
Saline	n=271	0.786 (0.727 to 0.844)	NS	6.91
Captopril		0.798 (0.743 to 0.852)		13.40

All AUCs differed significantly (<0.0001) from the AUC under the diagonal (identity) line. The optimal cutoff was the value of PA after the SAL that provided the highest accuracy, eg, the best tradeoff between sensitivity and specificity. The P values in the table relate to comparison of the CAPT and SAL. NS indicates not significant difference between tests.
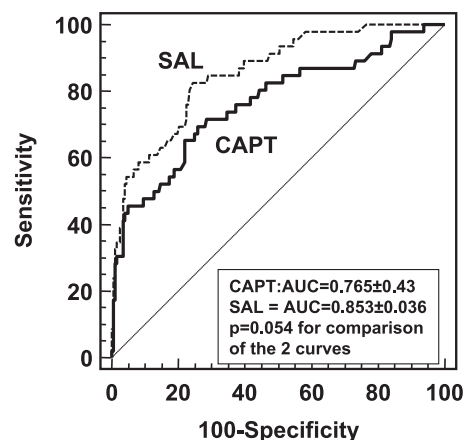

Figure 2. The plot shows the ROC of PA after the CAPT and the SAL for the identification of APA. The AUC under the SAL was higher than that under the CAPT, but the difference was borderline significant (inset).

CAPT:AUC=0.765±0.43
SAL = AUC=0.853±0.036
p=0.054 for comparison of the 2 curves

TABLE 4.   Operative Features (Definition Available in the Online Data Supplement) of the CAPT and the SAL for the Identification of APA According to an Na⁺ Intake Below or Above the Population Median

Na⁺ Intake	ROC Curve AUC (95% CI)	PA, ng/dL	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Positive Predictive Value	Negative Predictive Value
CAPT								
Below median	0.691 (0.601 to 0.772)	>15.9*	56.0 (34.9 to 75.6)	81.0 (71.7 to 88.4)	2.96	0.54	43.7	87.5
Above median	0.847 (0.771 to 0.906)	>13.4*	85.7 (63.6 to 96.8)	70.3 (60.4 to 79.0)	2.89	0.20	37.5	95.9
SAL								
Below median	0.849 (0.772 to 0.907)	>6.61*	84.0 (63.9 to 95.4)	75.8 (65.9 to 84.0)	3.47	0.21	47.7	94.
Above median	0.856	>11.3*	61.9	96.1	15.79	0.40	76.5	92.5

The sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values were calculated at the APA prevalence rate found in our patient cohort below and above median Na⁺ intake, which were 20.8% and 17.2%, respectively.

*This cutoff value corresponded with the highest accuracy, eg, the best combination of sensitivity and specificity.

Effect of Sodium Intake on the CAPT and SAL Performances

We found that the accuracy of the CAPT for the diagnosis of APA was higher at an Na⁺ intake above rather than below the population median (Table 4 and Figure S2 online). By contrast, the SAL accuracy was unaffected by Na⁺ intake. Hence, the borderline significant difference favoring the SAL over the CAPT became significant in the low sodium and waned in the Na⁺ half of the patients. The Na⁺ intake not only affected the aldosterone optimal cutoff values for both the CAPT and the SAL but also the operative features of both tests (Table 4).

Predictive Value of the CAPT and SAL

The positive predictive value and the negative predictive value for the CAPT and SAL as functions of the APA prevalence in the patients divided by Na⁺ intake are shown in Figure 3. In the patients screened at most referral centers, the APA prevalence is likely to be <50%; hence, both tests perform better at excluding than at confirming APA. Na⁺ intake had an impact on the predictive values: at a low Na⁺ intake, the SAL had a higher negative predictive value than the CAPT; at a high Na⁺ intake, the SAL had a higher positive predictive value but a lower negative predictive than the CAPT.

Discussion

Because the screening tests for PA have a low specificity, the selection of the PA patients for AVS requires demonstration of nonsuppressibility of aldosterone after dynamic testing. To this end, both the CAPT and SAL can feature ideal confirmatory tests,[21,32] but which test to prefer remains contentious, because they did not undergo a head-to-head comparison. Moreover, their performances were examined in few selected patients, mostly in comparison with another test that was used as the "gold diagnostic" standard.[4–6,14,33–40] Instead, they should be tested for accuracy at identifying APA, the only causes of PA that can be unequivocally diagnosed.[8] Thus, in the PAPY Study, as a conclusive diagnosis of APA was established with rigorous criteria,[1] we could evaluate of the diagnostic hyperformance of CAPT and SAL in the largest-series of APA ever reported.

Treatment Effects and Accuracy of End Points of the CAPT and SAL for Confirming APA

There was no significant treatment effect on hormone values either at baseline or after the CAPT and SAL, indicating that a long-acting calcium channel blocker and/or doxazosin does not markedly influence the aldosterone response to acute angiotensin-converting enzyme inhibition and volume loading. From the practical standpoint, this implies that these agents can be allowed during the CAPT and SAL to avoid the risks of uncontrolled HT.

Aldosterone decreased after the CAPT and SAL, but in the APA and IHA groups, it remained higher than in the PH patients, indicating that aldosterone after both tests carries a diagnostic gain over baseline data. The significant differences of AUC (from the diagonal AUC) for identification of APA, IHA, and PA for both tests (Table 3) confirm their diagnostic usefulness. However, at the plasma aldosterone value providing the highest accuracy for identification of APA, the sensitivity and specificity of the CAPT and the SAL were moderate. Overall, the accuracy of the SAL was borderline significantly (P=0.054) higher than that of the CAPT. The optimal plasma aldosterone cutoff value after the CAPT (13.9 ng/dL) was ≈2-fold higher than that (6.75 ng/dL) after the SAL, indicating that the latter test induces a much greater degree of suppression of aldosterone secretion than the former, at least within the time courses of the 2 tests. We cannot exclude that a greater aldosterone suppression could occur at a later time point after CAPT; however, this potential advantage has to be weighed against the costs and inconvenience of doubling the time of this test. Moreover, it has to be considered that these optimal cutoffs can differ slightly at other centers depending on several factors, including the aldosterone assay, the test conditions, the sodium intake, etc.

With either test, there was no increase of the AUC when the PRA- or cortisol-adjusted aldosterone values were used instead of the raw aldosterone values. Thus, our results do not confirm the contention that the measurements of PRA and cortisol improve the diagnostic accuracy of the SAL.[32]

A conclusive diagnosis of APA was largely unavailable in previous studies, because AVS and/or follow-up–based diagnostic criteria were not systematically used. Moreover, the diagnosis of PA was based on the SAL results itself, which introduced a tautology bias,[41] or the patients with severe HT,

Na⁺ intake above Median
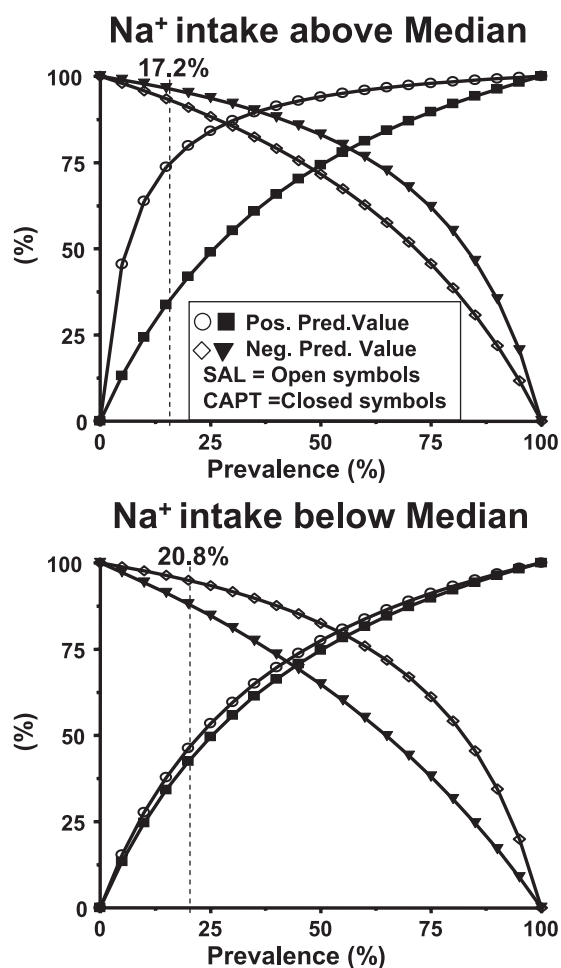

Na⁺ intake below Median

Figure 3. The plots show the positive and negative predictive values as a function of the prevalence (pretest or previous, probability) of APA in the patients divided into those above (top) and those below (bottom) the median (130 mEq per day) of Na⁺ intake. Predictive values were calculated at the sensitivity and specificity corresponding with the values of plasma aldosterone after the CAPT (15.9 and 13.4 ng/dL, respectively) and the SAL (6.61 and 11.3 ng/dL, respectively) that furnished the highest accuracy for the identification of APA in the low- and high-Na⁺ intake cohort. The plot shows that, under the most common rates of prevalence encountered in practice, as those seen in our low- (20.8%) and high- (17.2%) Na⁺ intake cohort (dashed vertical lines), the SAL performs better at ruling out rather than at confirming the presence of APA.

who compose a substantial proportion of the APA patients, were excluded. Recent studies with other tests as referents[22,26,42] did not confirm the high accuracy of the SAL originally reported[41]; studies evaluating the SAL versus the fludrocortisone test as a referent also concluded that the SAL was moderately accurate.[10,26,42]

The ARR after 25 mg of captopril, ie, half the dose used in our study, allowed identification of 6 PA patients with normal ARR baselines.[43] The same low dose was used in a head-to-head comparison of the CAPT with the oral Na⁺ loading where a post-CAPT aldosterone value of 8.5 ng/dL provided a high sensitivity (97%) close to that (100%) of the Na⁺ loading.[20] However, specificity and accuracy could not be determined, because there were only 5 patients with PH in that study; moreover, Na⁺ intake was not controlled during

the CAPT.[20] Thus, our results, consistent with previous studies, indicate overall that both the CAPT and the SAL are moderately accurate for identifying APA.

Accuracy of the CAPT and SAL According to Na⁺ Intake

A low Na⁺ intake activates the renin-angiotensin-aldosterone system and, therefore, might alter the results of the CAPT and SAL; however, Na⁺ intake was not taken into consideration in studies supporting use of these tests.[22,32] By splitting our patients according to the median of daily urinary Na⁺ excretion, we found that the SAL performed similarly in both cohorts. By contrast, the CAPT performance was markedly affected by Na⁺ intake: a <130 mEq per day Na⁺ intake resulted into a significant ($P=0.023$) decrease of the AUC (Figure S2). Thus, the fall of aldosterone after acute volume expansion is insensitive to dietary Na⁺ intake, whereas that in response to acute angiotensin-converting enzyme inhibition is affected by Na⁺ intake. From the practical standpoint, this implies that an Na⁺ intake >130 mEq per day should be recommended during the days before the test, because an Na⁺-restricted diet might impair the diagnostic accuracy of the CAPT.

Positive and Negative Predictive Values of the CAPT and SAL

The positive predictive value, eg, the probability that the disease is present when the test is positive, and the negative predictive value, eg, the probability that the disease is absent when the test is negative, can be most interesting for clinicians, because they allow determination of the performance of both tests in their own patient population. Figure 3 shows a plot of these predictive values for the CAPT and SAL as a function of APA prevalence. It shows that, at the prevalence of APA (<50%) seen at most referral centers, both tests perform better at excluding than at confirming the diagnosis, and, thus, they should be viewed as "exclusion" rather than confirmatory tests.

Not unexpectedly, the Na⁺ intake had affected the predictive values: at a low Na⁺ intake, the positive predictive value of the CAPT and SAL were similar, but the negative predictive value of the SAL exceeded that of the CAPT. At a high Na⁺ intake, the positive predictive value of the SAL was higher than that of the CAPT, but the negative predictive value of the CAPT exceeded that of the SAL.

Safety of the CAPT and SAL

Although we used a captopril dose that was twice that used previously,[20,24,43,44] the CAPT was well tolerated,[20] and caused neither significant hypotension nor changes of serum K⁺ (Table 2). Likewise, no adverse effects or changes of serum K⁺ were seen with the SAL, although a raise of BP was occasionally seen.

Limitations of the Study

Albeit done prospectively in newly diagnosed hypertensive patients referred to specialized HT centers, most patients investigated in the PAPY Study had, in fact, mild HT. Thus, how relevant the current findings are to a population with

more severe HT remains unknown. Moreover, the prespecified ARR of 40 used in the PAPY Study for the screening of PA is quite conservative. Hence, we cannot totally exclude that with such high ARR some APA could be overlooked. It might also be that few were misdiagnosed as IHA because of the tight criteria for identifying APA, the lack of availability of AVS at some centers, and the intrinsic insensitivity of dexamethasone-suppressed adrenocortical scintigraphy for diagnosing APA, as discussed.[1] Despite these limitations, because of the lack of accepted criteria to diagnose IHA, which, therefore, can only be presumed, there is no option other than to base investigation of diagnostic tests on the "firm ground" of the APA diagnosis. Thus, it is worth mentioning that our conclusions on the CAPT and SAL performances remained unchanged after restricting our analysis to the centers that performed AVS. Thus, the tight diagnostic criteria used for APA are strengths rather than weaknesses of this study.

It might also be argued that the CAPT and SAL performances were overestimated, because more than half of the patients were preselected for these tests based on the ARR results at baseline and after captopril. However, our protocol reflects common current practice, because these tests are mostly regarded as confirmatory. Moreover, the relatively large cohort of patients without PA investigated in this study represents a safeguard from this potential bias. Finally, because we excluded patients with heart and/or renal failure from this study, the safety of these tests under those conditions needs to be investigated.

Conclusions

This study allows the following conclusions: (1) even when applied to populations with enriched prevalences of PA, the accuracy of the CAPT and SAL is moderate, and false-positive and false-negative results are to be expected; (2) both tests are sensitive for the identification of APA, and their accuracy did not differ significantly at an adequate Na^+ intake; and (3) under the most common conditions of prevalence of APA, both the CAPT and SAL are more helpful at excluding rather than at confirming the presence of APA. Because captopril lowers BP, whereas the saline infusion might increase it, and because the CAPT is more simple and cheaper, it should be preferred to the SAL, provided that the patients are on Na^+ intake of ≥ 130 mEq per day (7.6 g of NaCl per day).

Perspectives

Because it is likely that the even the high prevalence rate of PA found in the PAPY Study underestimated the real prevalence of this disease,[1] future work should be aimed at determining the SAL and CAPT performances in patients selected based on lower cutoff values of the ARR versus those determined in the PAPY Study.

Appendix

A list of all Primary Aldosteronism Prevalence in Italy Study investigators is given in Table 5.

TABLE 5.   List of Participating Centers and PAPY Study Investigators

Center	Investigators
1. Padova, Italy, DMCS Internal Medicine 4	Gian Paolo Rossi, Andrea Semplicini, Chiara Ganzaroli, Achille Cesare Pessina
2. Padova, Italy, Endocrinology	Franco Mantero, Decio Armanini, Giuseppe Opocher, Paolo Sartorato
3. Ancona, Italy, Endocrinology	Gilberta Giacchetti, Vanessa Ronconi, Marco Boscaro
4. Reggio Emilia, Italy, Azienda Ospedaliera ASMN di Reggio Emilia Internal Medicine	Ermanno Rossi
5. Pisa, Italy, Internal Medicine	Giampaolo Bernini, Angelica Moretti
6. L'Aquila, Italy, Department of Internal Medicine and Public Health	Claudio Ferri, Giovambattista Desideri
7. Palermo, Italy, Internal Medicine	Giuseppe Andronico, Giovanni Cerasola
8. Brescia, Italy, Internal Medicine	Damiano Rizzoni, Enzo Porteri, Enrico Agabiti-Rosei
9. Legnano, Italy, Internal Medicine	Gaetana Palumbo, Carlo Costantini, Maria Teresa Lavazza
10. Rome, Italy, Internal Medicine	Claudio Letizia, Chiara Caliumi
11. Trieste, Italy, Internal Medicine	Bruno Fabris
14. Firenze, Italy, Endocrinology	Massimo Mannelli, Gabriele Parenti
15. Torino, Italy, Endocrinology	Mauro Maccario, Ezio Ghigo
17. Reggio Calabria, Italy, Nephrology	Francesca Mallamaci, Graziella Caridi, Carmine Zoccali
18. Bari, Italy, Internal Medicine	Anna Belfiore

Disclosures

None.

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